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Dissemination of a novel organ perfusion technique: initial multicentre experience of ex vivo normothermic perfusion of deceased donor kidneys

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Abbreviations

AKI	-	Acute kidney injury
CIT	-	Cold ischaemia time
COD	-	Cause of death
DAKT	-	Dual adult kidney transplant
DMII	-	Diabetes mellitus type 2
DBD	-	Donation after brain death
DCD	-	Donation after circulatory death
DGF	-	Delayed graft function
eGFR	-	Estimated glomerular filtration rate
EVNP	-	Ex vivo normothermic perfusion
HBI	-	Hypoxic brain injury
HD	-	Haemodialysis
HTN	-	Hypertension
ICH	-	Intracranial haemorrhage
IHD	-	Ischaemic heart disease
IQR	-	Interquartile range
MDRD	-	Modification of diet in renal disease
NHSBT	-	National Health Service Blood and Transplant
PD	-	Peritoneal dialysis
PMH	-	Past medical history
RBFi	-	Renal blood flow index
SD	-	Standard deviation
SPK	-	Simultaneous pancreas and kidney

TMA	-	Thrombotic microangiopathy
UO	-	Urine output
UTI	-	Urinary tract infection
UK	-	United Kingdom

Abstract

Warm machine perfusion technologies such as ex vivo normothermic perfusion (EVNP) are a promising means of organ preservation, assessment, and pre-conditioning prior to transplantation. The widespread use of EVNP in deceased donor kidney transplantation will require uptake in other units, but previous reports have not addressed how centres outside the originating unit might implement this new technique. We describe our combined approach to setting up a clinical EVNP service in two UK centres. Learning points and processes are outlined and discussed, including the need for robust protocols, training and staffing issues, and the need for a multidisciplinary approach. Our initial clinical experience is discussed, including the first reported uses of EVNP for dual kidney transplantation, for multi-organ transplantation, and for assessment of segmental parenchymal perfusion defects. Clinical outcomes of 12 deceased donor kidneys that underwent EVNP are described, along with the first analysis of outcomes from paired kidneys that had undergone static cold storage only. It is anticipated that this report will encourage the wider adoption of EVNP at other kidney transplant centres.

Introduction

The United Kingdom (UK) has seen significant improvements in deceased donor kidney transplantation over the past decade, with an increase in the number of deceased donors, especially donation after circulatory death (DCD) donors, and rising graft survival rates[1]. However, there are on-going issues in UK kidney transplantation that remain a cause for concern. Worldwide, many other countries face similar challenges.

The average age and co-morbidities of deceased kidney donors are increasing[1], and there still remains a disparity between the number of organs available from deceased donors and the number of patients on the transplant waiting list. This has cost implications, as there is a significant financial benefit associated with a patient receiving a transplant as opposed to continuing dialysis[2]. Furthermore, although kidney transplants from DCD donors have equivalent graft survival to those from donation after brain death (DBD) donors in the UK[3-5], transplants from DCD donors have a much higher rate of delayed graft function (DGF), and a higher rate of organ discard[6].

Warm organ perfusion technologies such as ex vivo normothermic perfusion (EVNP) may be able to successfully address some of these concerns. EVNP is a technique using paediatric cardiopulmonary bypass technology enabling the perfusion of an organ with a warm, oxygenated, erythrocyte-based solution prior to transplantation[7]. Studies suggest that EVNP reduces DGF in extended criteria donor kidneys when compared to historical controls preserved using cold storage alone[8]. Furthermore, the Cambridge group has reported the use of EVNP in successfully transplanting human kidneys that were deemed untransplantable and declined by all UK transplant units[9]. EVNP may therefore be able to reduce the rate of deceased donor kidneys that are unnecessarily discarded[6,10]. However, EVNP is a technically complex procedure, and reports have

been published from only two groups to date[9]. Like any new innovation in surgery, it is essential that novel perfusion technologies are widely translatable to other units.

The aims of this study are threefold. First, to present the combined early clinical outcomes of kidneys transplanted using EVNP from two centres new to the technique, including the only reported analysis of outcomes of paired kidneys from the same donor transplanted without EVNP. Second, to detail the key learning points for centres considering implementation of clinical EVNP, focussing on organisational and technical issues. Finally, the use of EVNP for hitherto novel indications is also described. The authors anticipate that this report will encourage the adoption of EVNP at other kidney transplant centres.

Methods

The evolution of a clinical EVNP programme at two units (Guy's Hospital, London (centre 1), and Freeman Hospital, Newcastle (centre 2)) in December 2015 is described. Both centres took similar approaches to implementing EVNP based on mentorship, step-wise training, and frequent evaluation. The timing of the steps below varied slightly due to variances in progression through local governance pathways. Both EVNP services had similar staffing led by a consultant transplant surgeon, with two or three surgical trainees providing additional support.

Clinical governance

Nationally, the NHS Blood and Transplant (NHSBT) Kidney Advisory Group[11] discussed the implications of EVNP expansion, and the consequences of a kidney that had undergone EVNP being subsequently declined for implantation and then offered to a non-EVNP centre. The Kidney Advisory Group approved the use of EVNP kidneys being offered back to the national transplant pool, if needed.

At hospital level, both new centres obtained local clinical governance approval for the use of EVNP via novel procedures committees. For both centres, advice was sought from local hospital departments including haematology (to approve the use of packed red blood cells from the blood bank), microbiology (to assess the risk of potential infection of the kidney during EVNP)[12-15], medical physics (to test and approve EVNP equipment), and operating theatre and anaesthetic staff (to provide the environment for clinical EVNP).

Transplant surgical colleagues within each department were consulted as to the potential clinical value of the new EVNP services. Demonstrations of the EVNP machine were undertaken for

colleagues in order for them to better understand the technique. Both centres engaged with local patient groups to raise awareness of EVNP, and the indications for its use. EVNP was only used after a discussion of the perceived risks and benefits was had with each patient and written consent was given. Patient information sheets were given to each patient prior to consent discussions (supplementary data; figure 1).

EVNP training

Both new centres first observed porcine kidneys undergoing EVNP at the Cambridge mentor centre. This involved observing the machine set up, drug preparation and administration, renal artery and vein cannulation, normothermic perfusion of the kidney, and vessel decannulation. Written EVNP protocols were scrutinised and learnt by both centres and members of the EVNP perfusion teams underwent dedicated supervised training days at the mentor centre. This involved a structured learning programme with progressive steps evaluated at each stage using a proforma. The programme covered knowledge of EVNP components, system set-up, priming, kidney cannulation, perfusion, decannulation and cold perfusion, disposal of consumables, data recording, and use of a kidney assessment tool using EVNP[16]. Staff from both centres were assessed against the proforma and, once deemed competent, were formally signed off as capable of independently performing the EVNP technique.

Training with untransplantable human kidneys

Before starting their clinical EVNP programmes, both centres performed EVNP on five human kidneys deemed unsuitable for transplantation that had been offered for research. This step enabled a safety check of the machine and EVNP process. Approval was obtained through NHSBT and local research ethics committees. During this phase, it became apparent that members of the EVNP

team should focus on specific tasks to ensure timely machine set-up and organ perfusion. The lead EVNP surgeon had responsibility for kidney bench work, vessel cannulation and decannulation, while the surgical trainees focussed on EVNP machine preparation and monitoring. An experienced member of the mentor centre EVNP team (SH) was present for warm perfusion of the first discarded kidney at both centres, to check competencies and offer advice. For each subsequent kidney EVNP, SH was available via telephone and video-teleconferencing facilities to advise and support, as the need arose. After five discarded kidney perfusions at each centre, SH discussed any learning points with the EVNP lead from each centre (CW and CC) before agreeing that clinical EVNP programmes could start. These programmes were in place before a randomised controlled trial of EVNP was initiated[7].

Indications for clinical EVNP use

Indications for EVNP of a deceased donor kidney prior to transplantation were: significant donor risk factors for DGF (e.g. expanded criteria donor, DCD donor, or donor acute kidney injury (Acute Kidney Injury Network stage 2 or 3[17])); or the need for viability assessment (e.g. sub-optimal cold flush of the kidney). Contraindications to the use of EVNP were: kidneys enrolled in a research study; injury or pathology not considered reversible by EVNP; multiple arteries not amenable to cannulation.

EVNP technique

The EVNP technique has been reported elsewhere[8,18]. Briefly, the EVNP circuit was based on commercially available paediatric cardiopulmonary bypass technology (Bio-Console 560, Medtronic, Watford, UK), with a heater (Chalice Medical, Nottinghamshire, UK), a combined heat

exchanger / oxygenator, and tubing (both Medtronic, Watford, UK). Hardware also included a flow transducer, temperature probe, and fluid infusion pumps (Figure 1). The renal artery and vein were cannulated and secured in place with 2/0 polyglactin ligatures. The kidney was placed in a sterile stainless steel chamber and perfused with heparinised red cell-based perfusate consisting of one unit of O Rhesus negative packed cells, 250 mL of Ringer's lactate, nutrients, dexamethasone, mannitol, insulin, prostacyclin, and bicarbonate.

The kidneys were perfused for 60 minutes at a pressure of 75 mmHg, and at 36^{o}C. Ringer's lactate replaced urine output mL for mL. During EVNP, perfusion pressure, urine output, renal blood flow, and perfusate temperature were recorded. Renal blood flow index (mL/min/100g) was calculated using the weight of the kidney before perfusion. Intra-renal resistance was calculated from the renal blood flow index and perfusate pressure. Arterial and venous blood gas samples were taken before perfusion, at 30 min and 60 min perfusion to ensure physiological conditions and to measure tissue oxygen consumption.

Each kidney was scored according to macroscopic appearance (1=excellent, 2=moderate/patchy, 3=poor), renal blood flow index (<50 mL/min/100g=1) and urine output (<43 mL/hr=1). This gave each kidney a total quality score of 1-5 (1-2=good; 3-4=moderate; 5=poor)[16]. If the kidneys scored 3 or less, they would be considered potentially suitable for transplantation after consultation with the on-call surgeon, with whom the final decision regarding implantation would lie.

Organ safety during EVNP was a prime concern. Before the clinical EVNP programmes started, both centres agreed that the occurrence of a major technical event would lead to a pause of their EVNP programme to enable discussion with the mentor centre and training, as needed. Major technical events were defined as any one of the following: unexpected decannulation of the kidney;

major leaks of perfusate from the circuit requiring use of additional packed red blood cells; and equipment malfunction leading to the possibility of organ hypo-perfusion. These were recorded prospectively.

Clinical data collection and analysis

Donor and recipient characteristics, and clinical outcome data, were recorded prospectively from kidneys that were transplanted after EVNP, and from paired kidneys from the same donor that had undergone static cold storage only. Kidneys undergoing EVNP from April 2016 to July 2017 were included; study follow-up ended on 1 May 2018.

Following transplantation, recipient serum creatinine and estimated glomerular filtration rate (four-variable Modification of Diet in Renal Disease (MDRD)) were recorded at one week, and one, three, six, and 12 months. If EVNP was associated with bacterial contamination of the kidney, it was felt that this would most likely manifest as an infected collection around the graft (i.e. an organ/space surgical site infection[19]). Data on infected perinephric collections within three months of transplantation were recorded prospectively.

Delayed graft function (DGF) was defined as the need for dialysis, for any cause, in the first 7 days post-transplantation[20]. Duration of DGF was defined as the number of days from transplantation to the last day of dialysis. Primary non-function was defined as failure of the graft to ever function following transplantation, regardless of cause. Graft failure was defined as return to dialysis or graft nephrectomy, whichever occurred first, and was censored for death. Cold ischaemia time (CIT) was defined as the period from the start of cold perfusion in the donor to reperfusion with blood within the recipient (i.e. including the EVNP duration).

Where one kidney from a donor was implanted after EVNP and the paired kidney was transplanted after static cold storage only, characteristics and post-transplant outcomes were compared. Groups

were compared using Fisher's exact and chi-squared tests for nominal data, the Mann-Whitney test for ordinal or non-parametric continuous data, and Student's t-test for parametric continuous data.

Results

Insights during the learning phase of EVNP using discarded kidneys

Between December 2015 and February 2016, both centres underwent the learning phase of EVNP using five discarded kidneys. Both centres reported no major technical events during EVNP in this phase. During this learning process, three practical issues became apparent.

Firstly, three personnel were ideally required during the EVNP. Two scrubbed surgeons (one trained in EVNP) were needed at kidney cannulation and subsequently at decannulation and cold flushing. The third (unscrubbed) team member operated the machine, administered drugs and fluids, and recorded data. Secondly, set up of the EVNP machine and circuit took longer than initially anticipated, with average times of 90 minutes. Finally, preparation time was further prolonged if the kidney had multiple vessels arising from the aortic patch. This required end-to-side anastomosis of the smaller artery to the main artery to create a single orifice for cannulation. Use of the right kidney for EVNP required preparation of the attached inferior vena cava with ligation of side branches and oversewing of the infrahepatic inferior vena cava and left renal vein orifices. Hence, this initial phase was a critical learning process, not only in the specific practical aspects of performing EVNP but also in appreciating the need to complete the organ preparation, machine set-up, and organ perfusion steps in a timely manner.

During this phase, a checklist was adopted by centre 1, with the aim of decreasing machine set-up times, and reducing the risk of technical events (Supplementary data, Figure 2).

Clinical EVNP experience

Between 1 March 2016 to 31 July 2017, EVNP was performed on 14 kidneys from 12 donors (11 kidneys in centre 1, three kidneys in centre 2). Of the 14 kidneys that underwent EVNP, 12 organs were implanted into 10 recipients. Two pairs of kidneys were implanted as dual grafts and one

kidney was implanted simultaneously with a pancreas. The remaining seven kidneys were transplanted as single allografts (Table 1).

Two kidneys from two different donors were not implanted following EVNP; the first kidney (organ 6, Table 1) scored 3 on EVNP and was deemed unsuitable for the intended recipient (the contralateral non-EVNP kidney was not implanted for the same reason). The second kidney (organ 8, Table 1) was not transplanted as the recipient had a significant anaesthetic complication requiring the transplant to be cancelled. This kidney was intended to be implanted as a dual graft, but only one kidney had completed EVNP before the transplant was unexpectedly cancelled. These two kidneys were subsequently offered to other centres but were declined by all centres due to prolonged CIT and were discarded.

Table 1 shows the donor and recipient characteristics for each kidney that underwent EVNP. Median (IQR) donor age was 65 (48-69) years, and nine (64%) were DCD donors. The indications for EVNP were viability assessment (n = 6) and/or reduction of DGF (n = 11). Median (IQR) recipient age was 54 (39-60) years.

Organ assessment parameters on EVNP, and subsequent CITs are shown in Table 2. Kidneys underwent EVNP for a median (IQR) duration of 60 (59-60) minutes, and the median (range) EVNP viability score was 1 (1-3). Oxygen consumption was measured in 5 kidneys. Median (IQR) oxygen consumption was 59.6 (40.4-93.8) mL/min/g. Renal blood flow index was measured throughout perfusion and showed a gradual increase during EVNP (Figure 2). Mean (SD) CIT was 14:45 (2:27) hours:minutes for kidneys implanted as single grafts. The mean (SD) time from the end of EVNP to re-perfusion of single kidney-only transplants in the recipient was 3:24 (2:49) hours:minutes. Centre 1 did not to begin the recipient operation until the organ was fully assessed

during EVNP (as the majority were performed for viability assessment) and therefore had a relatively longer CIT following EVNP (mean (SD) 309 (151) minutes). Centre 2 began the recipient operation during organ perfusion, leading to a shorter CIT following EVNP (mean (SD) 65 (11) minutes).

Additional learning points during early EVNP clinical experience

Performing EVNP on kidneys for clinical transplantation provided additional learning points. In smaller theatres, it was challenging for EVNP to take place during the recipient's operation. Another theatre was therefore required, limiting the ability to perform EVNP during working hours when theatre capacity was limited. In addition, two technical issues were encountered at centre 1. One kidney had an unplanned arterial decannulation, which was rectified within two minutes by re-cannulation. Subsequently, tying the ligature around the artery to another ligature around the proximal cannula prevented this from reoccurring. On another occasion, the kidney cradle venous outflow pipe became occluded due to an air lock, resulting in a depletion of the circulating volume, with subsequent organ hypoperfusion. The kidney underwent early decannulation after 45 minutes of EVNP and was then implanted. After this, the draining tube from the venous reservoir to the cradle was regularly checked and manipulated to improve drainage. Technical issues experienced during machine set-up, or organ perfusion, along with possible causes, are shown in Table 3.

Recipient outcomes

In the ten recipients that received kidneys that had undergone EVNP, there were no cases of primary non-function. Three patients experienced delayed graft function (30%), for between 5-8 days duration. Median (IQR) inpatient stay was 10 (8-14) days. Patient and graft survival was 100% at one year, with median (IQR) eGFR of 52 (35-63) mL/min/1.73m^2 at 6 months, and 53 (40-62)

mL/min/1.73m^2 at 12 months. There were no serious adverse events attributable to EVNP in our patients. There was one instance of an infected deep perinephric collection following implantation of an EVNP kidney. However, this collection was originally sterile, but, following repeated percutaneous drainages, became secondarily infected. This was treated successfully with intravenous flucloxacillin.

Post-transplant outcomes of single kidneys implanted after undergoing EVNP were compared with those of the non-EVNP contralateral kidney from the same donor (Tables 1 and 3). The pair of kidney 8 was not transplanted due to severe parenchymal retrieval damage, and therefore kidney 8 was excluded from this analysis. There was no statistically significant difference in recipient demographics between the two recipient groups. The CIT was significantly longer in kidneys receiving EVNP compared to static cold storage (mean (SD) 843 (105) vs. 608 (167) minutes; p=0.011). There were no statistically significant differences in the rates of primary non-function or DGF between the two groups (p=1.00, p=0.56, respectively). Statistical analysis of DGF duration could not be performed, as there was only one episode of DGF in the EVNP group. There was no difference in graft function between the two groups at one week and one-, three-, six- and 12-months post transplantation (p=63, p=0.58, p=0.71, p=0.74, p=0.22, respectively).

Novel uses of EVNP

EVNP in dual adult kidney transplantation (DAKT): Centre 1 performed the first reported cases of DAKT after sequential EVNP on both kidneys (kidneys 1 and 2, and 4 and 5 on Table 1). The first recipient had immediate graft function, with good graft function at 12 months post-transplant (creatinine 122 µmol/L, eGFR 53 mL/min/1.73m^2). The second recipient received kidneys that had been declined by another unit due to sub-optimal cold flush. The kidneys perfused well on EVNP

with viability scores of 1 and 2, respectively. However, this recipient had DGF of 8 days duration, and kidney transplant biopsies at day 5 post-operatively demonstrated acute thrombotic microangiopathy (TMA). Blood tests were unable to identify any underlying causes for the TMA such antibody-mediated rejection, atypical haemolytic uraemic syndrome or procoagulant disorders. The patient was treated with plasma exchange and intravenous immunoglobulins. Repeat biopsy at day 12 post-transplantation showed resolution of TMA. Oral tacrolimus was continued as tacrolimus-related TMA was thought to be highly unlikely due to the early onset. The patient has poor graft function at 12 months post-transplantation (creatinine 340 μmol/L, eGFR 12 mL/min/1.73m^2) but remains dialysis-independent.

EVNP in simultaneous kidney transplantation (SPK): Centre 1 also performed the first reported kidney EVNP before SPK transplantation (kidney 11, Table 1). The recipient had immediate graft function and good function at 6 months post-transplantation (creatinine 126 μmol/L, eGFR 44 mL/min/1.73m^2). Unfortunately, the patient developed post-transplant lymphoproliferative disorder four months post-operatively and is receiving chemotherapy.

EVNP in the assessment of vascular injury: During procurement of a kidney from a 40 year-old DBD donor, the renal artery was incised 1 cm from the renal hilum. The renal artery was cut through 50% of its circumference at the bifurcation into segmental arteries (Figures 3a and 4b). Vascular reconstruction of the injury was not possible without ligation of one of the branches. However, the effect of ligating one of the branches on parenchymal and ureteric perfusion was not known. The decision was therefore made to ligate the branch, repair the injury and assess the perfusion deficit during EVNP. Therefore, one branch was ligated and the renal artery was reconstructed using 6-0 Prolene (Figure 3c). There was no significant bleeding from the repaired

vessels, and the renal parenchyma re-perfused well anteriorly (Figure 4a). There was a small perfusion deficit at the posterior-superior aspect of the kidney (Figures 4b and c), comprising <10% of the renal parenchyma. The ureter was well perfused, and the kidney was transplanted (kidney 10, Table 1). The recipient's lowest creatinine was 222 μmol/L at four months post-transplant; deteriorated graft function led to a graft biopsy that showed recurrent membranous nephropathy.

Discussion

EVNP is a promising technique that may enable deceased donor kidney to undergo pre-conditioning and viability assessment. However, if the early potential of this technology is to be realised outside the originating centre, the technique will need to be readily translatable to other units. This multi-centre observational study details the key organisational issues of establishing a clinical EVNP service. A defined training pathway enabled clinical EVNP services in two UK centres to be established after a learning curve with five non-transplantable deceased donor kidneys. Technical challenges became apparent, but were readily overcome. Twelve kidneys were transplanted into 10 recipients after EVNP. The rate of DGF was 30%, with no complications attributable to the EVNP technique.

The introduction of a clinical EVNP service requires a multimodal approach, including governance, logistical, and training considerations. Given that it was possible that organs would be declined for transplantation after undergoing EVNP, it was felt important that other centres in the UK were made aware of the implications of receiving such an organ. These discussions focussed on the potential loss of the aortic patch and shorter vessel length in the donor kidney due the need for EVNP cannulation insertion. Extensive discussions with local haematology departments were also needed to ensure that any units of packed red blood cells used during EVNP were attributed to the correct recipient, even if an organ was declined after EVNP and transported to another kidney transplant centre.

EVNP logistical issues are challenging. The procedure is undertaken in theatre; ideally in the same theatre that the transplant will take place. The equipment and personnel needed for EVNP currently take up enough space to cause problems if simultaneous transplant surgery is undertaken in a small

theatre. Ideally, a dedicated perfusion theatre would be used, though it seems likely that further evidence of the benefit of EVNP will be required before most transplant units would consider such an investment of space and resources.

The EVNP technique itself was readily learnt, aided by a structured learning approach and formal assessment criteria. It was felt that this strategy, along with EVNP of discarded human kidneys, provided sufficient capability for the clinical programme to be initiated. EVNP remains a complex technique, however, and even with this experience, it was inevitable that some technical issues would arise. A close relationship with the mentor centre was essential, along with ready access to out-of-hours expertise. The use of a checklist reduced inefficiencies in the machine set-up process, and provided reassurance that essential steps had been completed. Even with these systems in place, it is likely that only larger kidney transplant units will be able to staff an EVNP service that uses current technology. These considerations may mean that smaller centres may wish to transport selected deceased donor kidneys to regional 'perfusion hubs' for EVNP to be undertaken, before being transported back to the referring centre [21].

In order to reduce the risk of significant bleeding from the kidney at the start of EVNP, back-table preparation must be meticulous. Retrieving the right kidney with a tube of IVC enabled cannulation of the IVC at the confluence, preserving the length of the venous outflow. Arterial cannulation was complex if there were multiple renal arteries. The implanting surgeon must be willing to accept a kidney with no aortic patch, as the arterial cannula ligature site is routinely excised after EVNP. The introduction of effective patch clamps may avoid this issue, in future.

At present, the main indications for EVNP are to attempt to reduce DGF, and to assess organ viability (e.g. those with poor cold perfusate flush). Kidneys from donors with significant AKI may benefit from EVNP for both of the above indications. DGF occurs in approximately 25% of kidney transplants from DBD donors and approximately 50% of DCD kidney transplants[5]. DGF is associated with prolonged length of stay and the need for graft biopsies. In DBD kidney transplantation, DGF is also associated with acute rejection[22], chronic allograft dysfunction[23] and graft loss[22,24]. A randomised controlled trial of EVNP use in DCD kidney transplantation is currently underway in the UK[7], and results are awaited with interest.

In this series, 30% of patients had DGF, despite the use of organs from older, predominantly DCD, donors. There were no instances of graft or patient loss within the follow-up period, and early graft function was good. There were seven donors where one kidney received static cold storage and EVNP, and the other received static cold storage alone. Although there was a trend towards lower DGF and primary non-function rates in the EVNP group, this did not reach statistical significance. These results are encouraging, however, and are the first paired analyses to be published[8]. Importantly, there were no complications in our series that were attributable to EVNP (e.g. infected perinephric collections, vascular thrombosis). A previous study has shown that a significant proportion of cultures taken from warm perfusate during EVNP grew bacteria, though these are of doubtful clinical significance[12,15]. Given uncertainties about appropriate doses, and the underlying rationale, antibiotics are not given during EVNP.

Other clinical scenarios where EVNP may be beneficial are described above, for the first time. DAKT and SPK transplants are prolonged operations, often in recipients with multiple co-morbidities. Avoidance of DGF makes post-operative fluid management more straightforward, and

might avoid the associated adverse cardiovascular and tissue healing implications associated poor graft function. Primary renal graft function in the SPK recipient was surprising, given the donor history of significant AKI, and suggests that EVNP was beneficial in this case. We note that the second DAKT recipient developed TMA, with no apparent underlying cause. To the best of our knowledge, this has not been reported in any other recipient of a kidney that has undergone EVNP, and therefore it would appear unlikely that the EVNP technique was a causative factor.

This study also demonstrates the potential for EVNP to assess vascular injuries and perfusion deficits. Injury to the kidney occurs in 7.1% of procurement procedures in the UK[25] and often results in organ discard. Polar arteries appear to be at greatest risk of vascular injury[26]. This novel indication for EVNP has the potential to increase the donor pool, as there are currently no established means of assessing organ damage beyond checking for leaks using cold fluid flush. A significant perfusion deficit or compromise of the ureteric blood supply[27] would have allowed the surgeon to make an informed decision whether to proceed with implantation or not. Assessment during EVNP also enables the integrity of the vascular repair to be examined. Other novel indications for EVNP are under investigation, including its use in prolonged preservation[28], manipulation of organ immunogenicity[29-32], and delivery of pharmacological[33-38] or temperature-dependent interventions (e.g. cellular therapies[39]).

We acknowledge the weaknesses of this study. Whilst we have detailed the process necessary for two centres to establish EVNP, these may not fully reflect processes outside of the UK. As with any early experience, patient numbers were small, and larger groups and longer follow-up may be necessary to detect events in survival analyses.

This study has demonstrated the challenges of introducing a new perfusion technology and has described a pathway that we hope other kidney transplant units will find valuable. EVNP is a complex technique, but can rapidly be learnt if appropriate training and mentoring is available from an experienced centre. Early experiences suggest that EVNP is a safe technique, and that graft and patient outcomes are acceptable. The indications for kidney EVNP are expanding, and EVNP is likely to be an increasingly useful tool in the transplant surgeon's armamentarium.

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Author Contribution Statements

P.C and B.P contributed equally to conduction of EVNP, data collection, analysis and writing of the manuscript. R.U. conducted EVNP, and L.B., I.I, A.S, and R.F conducted EVNP and collected data. S.H, and M.L.N., set up and conducted training at the mentor centre and advised on the introduction of EVNP at the two new centres. C.W. and C.J.C. conducted EVNP and led the EVNP programmes in Newcastle and London, respectively. J.O., C.W., S.H., M.L.N., and C.J.C. wrote and edited the manuscript.

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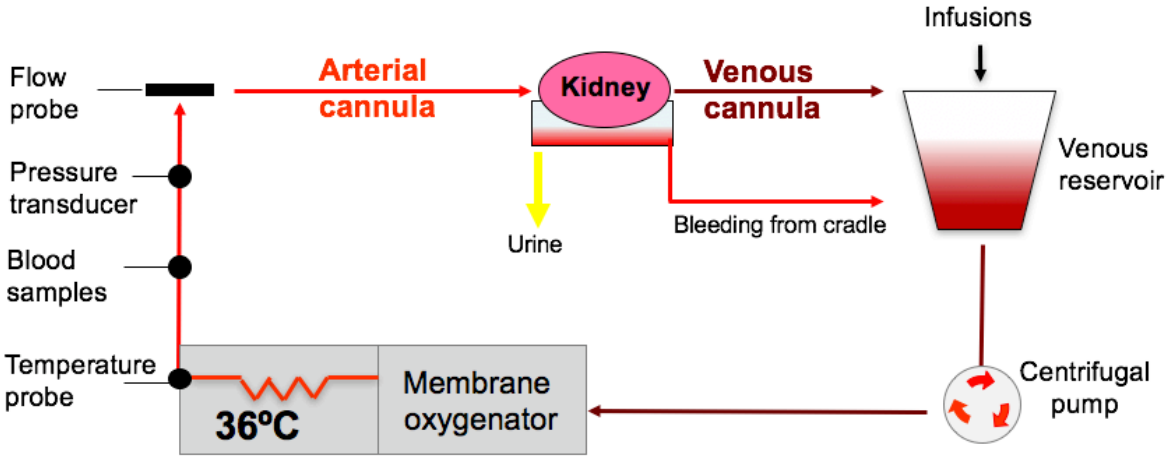

Figure 1: Ex vivo normothermic perfusion (EVNP) circuit components. This figure shows the schematic arrangement of the main components of the EVNP perfusion system with the arrows indicating direction of blood flow.

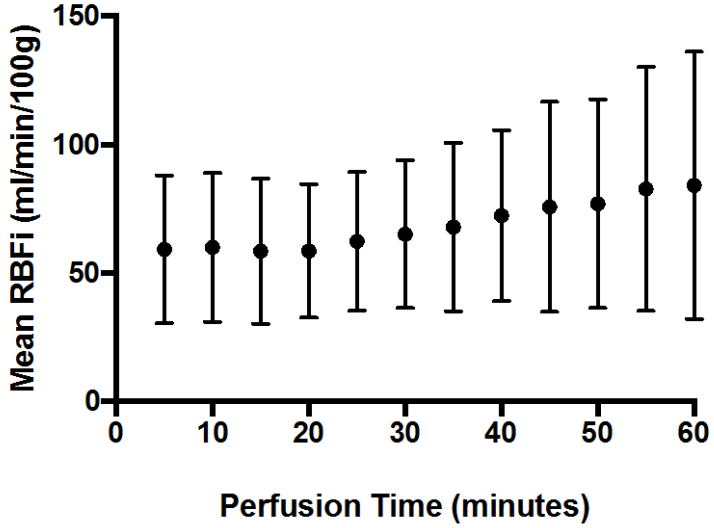

Figure 2*:* Mean (SD) renal blood flow index during ex vivo normothermic perfusion (n=14 kidneys)

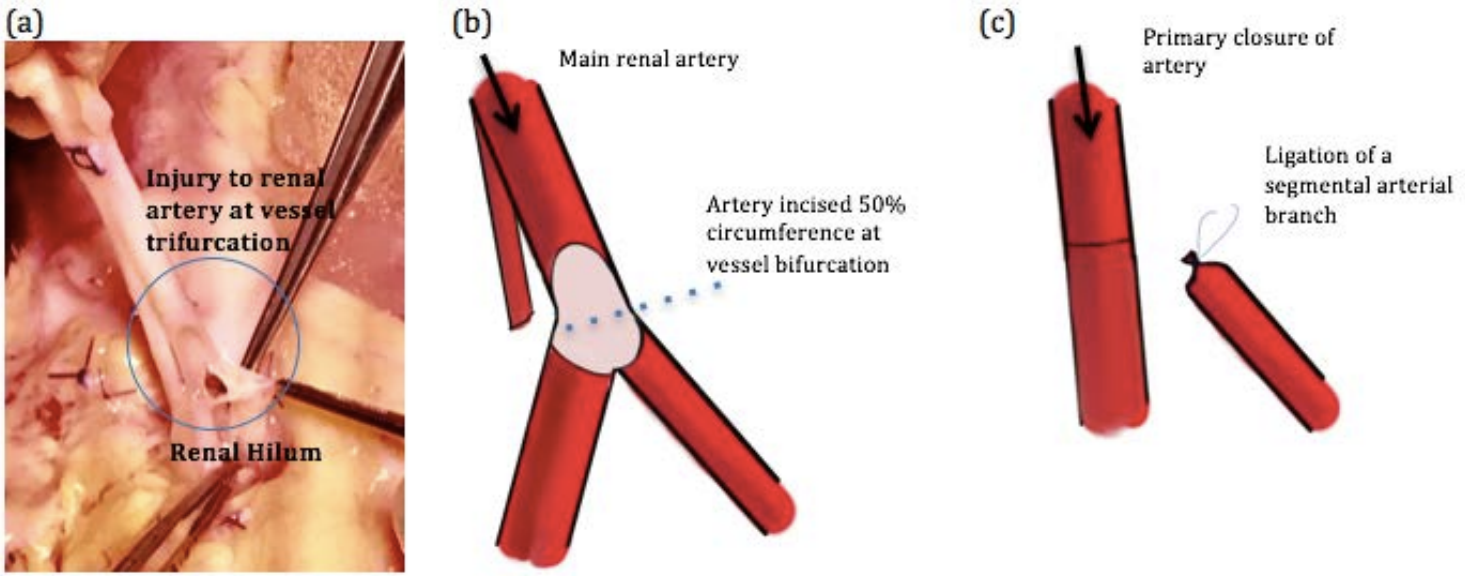

Figure 3: (a) Retrieval injury of the right renal artery. 50% of the artery circumference ligated at the bifurcation. (b) Diagram of renal artery injury (c) Repair of the right renal artery: one branch ligated, with primary closure of the remaining vessel

(a) (b) (c)

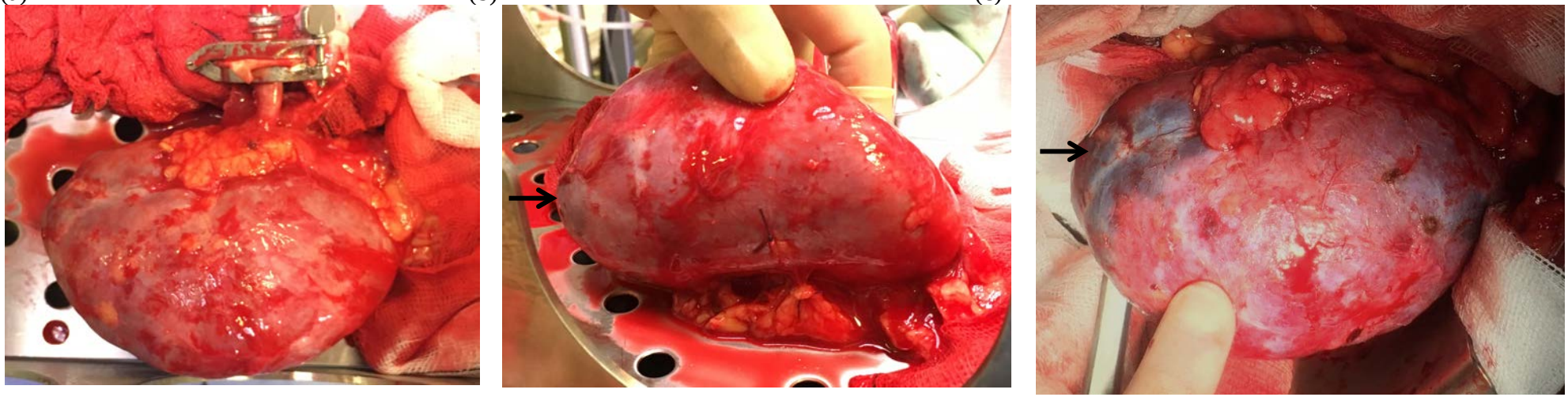

Figure 4: (a) Anterior aspect of the kidney during EVNP: global perfusion (b) Posterior aspect of the kidney during EVNP: upper pole perfusion defect of the renal parenchyma detected (<10%) marked with black arrow. (c) Posterior aspect of the kidney after implantation into the recipient: upper pole perfusion defect marked with black arrow.

Organ number	Donor type	Indication (s) for EVNP	Donor age / sex	Donor COD	Donor PMH	Organ side, findings	Visual score (1-3)	RBFi (ml/min /100g)	UO (ml/hr)	EVNP score (1-5)	O_2 consu-mption (ml/min /g)	Time on EVNP (min)	CIT (hr:min)	Recipient number and transplant type	Recipient age / sex	Dialysis status	DGF duration (days)	Paired analysis
1	DCD	Viability assessment and reduction of DGF	69F	HBI after cardiac arrest	Terminal creatinine 202 umol/L (no baseline)	R	1	81	150	1	Not recorded	68	20:18	1 – Dual	60M	HD	0	No
2						L	2	23	50	2	Not recorded	60	20:48					No
3	DCD	Reduction of DGF	66M	Pneumonia and resp. failure	COPD	R	1	59	80	1	Not recorded	55	13:40	2 – Single	54F	PD	0	Yes
4	DCD	Viability assessment and reduction of DGF	66F	ICH	HTN (2 agents), DMII, meningioma	L, poor cold flush	2	46	120	2	Not recorded	65	22:30	3 – Dual	58F	HD	8	No
5						R, poor cold flush	1	63	160	1	Not recorded	53	24:00					No
6	DCD	Reduction of DGF	71M	HBI after cardiac arrest	HTN (2 agents)	R	3	29	55	3	26.6	60	Organ not implanted (EVNP score 3)					No
7	DBD	Viability assessment and reduction of DGF	17F	HBI after cardiac arrest	Asthma, bronchie-ctasis AKIN stage 2	R	2	120	25	2	112.1	60	14:00	4 - Single	28M	HD	0	Yes
8	DBD	Viability assessment and reduction of DGF	55F	HBI after cardiac arrest	AKIN stage 3, IHD	R	3	50	15	3	Not recorded	60	18:44	5 - Single	54M	PD	5	No
9	DBD	Reduction of DGF	76F	ICH	HTN	L	1	97	190	1	54.1	60	Intended as a DAKT. Organ not implanted (named recipient had significant anaesthetic complication)					No

10	DBD	Viability assessment – injury to renal artery	40F	HBI after cardiac arrest	None	R	1	83	83	2	59.6	60	16:21	6 – Single	42M	HD	5	Yes
11	DBD	Viability assessment and reduction of DGF	21M	Trauma	AKIN stage 3	L	1	183	212	1	59.6	60	13:11	7 - SPK	29F	HD	0	Yes
12*	DCD	Reduction of DGF	53F	ICH	None	L	1	89	555	1	Not recorded	60	10:52	8- Single	61M	Pre-emptive	0	Yes
13*	DCD	Reduction of DGF	51M	ICH	HTN, UTIs,	L	1	112	210	1	Not recorded	60	14:09	9 - Single	48M	HD	0	Yes
14*	DCD	Reduction of DGF	64F	ICH	None	L	1	76	360	1	Not recorded	60	13:35	10 - Single	64M	HD	0	Yes

* Kidneys implanted by centre 2.

Acute kidney injury (AKI) categorized according to the Acute Kidney Injury Network (AKIN) stage, cold ischemia time (CIT), cause of death (COD), donation after brain death (DBD), Dual adult kidney transplant (DAKT), donation after circulatory death (DCD), delayed graft function (DGF), diabetes mellitus type 2 (DMII), ex vivo normothermic perfusion (EVNP), hypoxic brain injury (HBI) hemodialysis (HD), hypertension (HTN), intracranial hemorrhage (ICH), ischemic heart disease (IHD), peritoneal dialysis (PD), past medical history (PMH), renal blood flow index (RBFi), simultaneous pancreas kidney (SPK), urine output (UO), urinary tract infection (UTI)

Table 1. Donor, recipient, EVNP, and clinical characteristics for each kidney undergoing ex vivo normothermic perfusion (EVNP) in both centres

Abnormal findings	Possible causes
Reduced organ perfusion	• Air lock (bubble) within arterial cannula • Blood pooling in cradle, with reduced flow back into venous reservoir • High intra-renal (parenchymal) resistance
Accidental arterial decannulation	• Loosely tied ligatures between cannula and vessel • Excessive traction on cannula
Abnormal pressure readings	• Leaks within the pressure line system • Incomplete de-airing of centrifugal pump chamber • Manometer improperly calibrated prior to organ perfusion start
Perfusate temperature <36^{o}C	• High intra-renal resistance with low perfusate flow, leading to excessive cooling • Heat exchanger fluid not circulating

Table 2: Abnormal findings during ex vivo normothermic perfusion set-up and/or organ perfusion, and possible causes.

Variable	EVNP kidneys n=7	Static cold storage n=7	p value
Recipient age (years)	48 (29-61)	57 (31-61)	1.00†
Recipient male sex	5 (71%)	5 (71%)	1.00*
Pre-transplant mode of dialysis			
None	1 (%)	0 (0%)	0.51‡
Haemodialysis	5 (%)	5 (60%)	
Peritoneal dialysis	1 (%)	2 (40%)	
Cold ischaemia time (minutes)	838 (105)	608 (167)	0.01§
Primary non-function	0 (0%)	1 (20%)	1.00*
Delayed graft function	1 (14%)	3 (43%)	0.56*
Death-censored graft survival at 1 year	100%	86%	0.31¶
1 week eGFR (mL/min/1.73m^2)	24 (18)	30 (31)	0.63†

1 month eGFR (mL/min/1.73m^2)	47 (14)	53 (24)	0.58†
3 month eGFR (mL/min/1.73m^2)	46 (14)	50 (20)	0.71†
6 month eGFR (mL/min/1.73m^2)	51 (14)	48 (19)	0.74†
12 month eGFR (mL/min/1.73m^2)	59 (15)	53 (21)	0.64†

Data expressed as mean (SD), median (IQR), number (%)
*Fisher's exact test, †independent t-test, ‡Chi-squared test, §Mann-Whitney U test, ¶Log rank. Estimated glomerular filtration rate (eGFR) analysis excludes graft failure

Table 3: Paired analysis between kidneys undergoing ex vivo normothermic perfusion (EVNP) and those undergoing static cold storage only

Warm blood flow before kidney transplantation (EVNP)

We would like to inform you about a new treatment that may help to make your transplanted kidney work more quickly. This leaflet explains more about warm blood flow (ex vivo normothermic perfusion or EVNP), including the benefits, risks and any alternatives, and what you can expect when you come to hospital.

The information will help you decide whether this treatment is right for you. If you have any further questions or concerns, please contact us using the contact details on the back of this leaflet.

What happens to a donor kidney before it is transplanted?

When a kidney is removed from a deceased donor the blood is flushed out of it with a cold liquid and then it is stored in a box of ice until it is ready to be transplanted. This process is called 'static cold storage'. Static cold storage has been used in kidney transplantation for more than 30 years, and is both simple and effective. It is therefore the standard procedure used in most transplant centres around the world.

Static cold storage, however, does not preserve the kidney perfectly, and there is still some damage to the kidney that gets worse the longer the kidney is stored. This may mean that the kidney takes longer to 'wake up' and start working after the transplant. Around half of patients who receive a kidney transplant from a deceased donor may need to wait a while for the kidney to start working. This can take a few days or sometimes a few weeks.

What is warm blood flow (EVNP)?

An alternative to static cold storage is to pump warm blood through the kidney for about an hour before it is transplanted into you. This procedure uses a machine similar to the one used during open-heart surgery often referred to as a 'bypass machine'. The bypass machine looks like a small dialysis machine and consists of a pump, tubing, and some equipment to warm the blood and expose it to oxygen. The blood that is used is stored blood that has been previously donated by blood donors. Once the process is finished, the blood is flushed out of the kidney. Every part of the machine that touches the kidney remains sterile. This process is called EVNP.

The purpose of EVNP is to provide blood and oxygen to the kidney before it is transplanted into you. This allows the kidney to recover from some of the damage caused by cold storage.
EVNP has been used successfully in Leicester, and the transplant team at Guy's would like to introduce it here. Using EVNP in Leicester, only 1 out of 18 patients had transplanted kidneys that were slow to wake up and start working after the transplant.

Why is this treatment being suggested for my kidney transplant?

A patient with a kidney transplant that is slow to wake up needs dialysis until it starts to work. They may feel unwell due to build-up of toxins (poisons) in their body. These patients need regular ultrasound scans until the kidney starts working, and are likely to need one or more kidney biopsies (have tissue samples taken) to make sure that the kidney is not being rejected by their body. With any kidney biopsy there is a small risk of bleeding and of damage to the kidney. The biopsy procedure can also be uncomfortable, as the patient must remain lying flat for four to five hours afterwards. Patients with kidney transplants that are slow to wake up spend a longer time in hospital because of the need for extra ultrasound scans and biopsies.

The expected benefit of EVNP is that it increases the chance that your kidney will work straight away after the transplant. This will avoid the need for extra ultrasound scans and kidney biopsies, and will help get you home from hospital more quickly.

Sometimes EVNP is used to check that the blood flow through the kidney is good and to see if the kidney can make urine while it is attached to the EVNP machine. If the blood flow is good and the kidney makes urine while on the EVNP machine, this can give the transplant surgeons more confidence that the kidney is suitable for transplantation.
The EVNP team will explain why they think that EVNP would be helpful to you and your kidney.

What are the possible risks?

All medical procedures carry some risk. It is possible that EVNP may introduce infection into the kidney, or damage it in some other way that we can't yet predict. In the Leicester patients there were no unusual infections, bleeding problems, or damage to the kidneys resulting from the procedure.

Are there any alternatives?

If you decide not to allow your future kidney transplant to undergo EVNP it will be stored in the usual way in cold liquid in the icebox until your operation.

Sometimes, EVNP might be used if the transplant surgeons are concerned about the chance of poor blood flow in the kidney after transplantation. If this is the reason for recommending EVNP, and you decide not to allow the kidney to undergo EVNP, there may be an increased risk of poor blood flow in the kidney. The transplant surgeon looking after you will tell you if they think that EVNP is needed, or if static cold storage is an acceptable option for your kidney.

How many times has this been done at Guy's before?

This is a new treatment that we have introduced at Guy's. We will tell you how many times EVNP has been used at Guy's when we discuss the treatment with you and seek your consent

Consent - asking for your consent

We want to involve you in decisions about your care and treatment. If you decide to go ahead, you will be asked to sign a consent form. This states that you agree to have the treatment and you understand what it involves.

If you would like more information about our consent process, please speak to a member of staff caring for you.

What will happen next?

The kidney will be attached to the EVNP machine for about an hour. The transplant surgery and the rest of your treatment after the transplant will be as usual, and you will not need any extra tests or extra clinic visits. The transplant team and Mr Callaghan will monitor you closely to detect any possible problems that might be due to the EVNP treatment.

Your decision whether or not to choose this new treatment will not affect any other aspect of the care that you will receive before, during, or after the transplant.

Figure 1 – Patient information sheet for ex vivo normothermic perfusion (EVNP). Logos and contact details have been removed from this document prior to submission to the journal.

Before EVNP

Have the team members introduced themselves and confirmed roles?
Yes ☐

Confirm the correct organ for the correct recipient
Yes ☐
N/A – no recipient selected yet ☐

Has the patient consented for EVNP?
Yes ☐
N/A – no recipient selected yet ☐

Does the patient have any known drug allergies?
No ☐
Yes ☐ _____

Does the patient have special blood requirements?
No ☐
Yes ☐ Irradiated blood ☐
CMV neg blood ☐

Is all equipment and disposables available for EVNP?
Yes ☐

Before cannulation

Has heparin 3000 units been given?
Yes ☐

Are all bungs tight, with no leaks?
Yes ☐

Is O_2 flowing at the correct rate?
Yes ☐

Is temperature within range?
Yes ☐

Have blood transfusion checks been performed?
Yes ☐

Has the pressure line been calibrated and the flow-probe in correct direction?
Yes ☐

Are oxygen, haemoglobin, and pH within range on blood gas analysis?
Yes ☐

Has the kidney been flushed with cold saline?
Yes ☐

Is there cold preservation fluid, iv giving set, and a bowl of ice ready in case of rapid unplanned return to cold storage?
Yes ☐

Before decannulation

Have the intended blood samples been taken?
Yes ☐
Not applicable ☐

Is cold preservation fluid, iv giving set and a bowl of ice ready?
Yes ☐

Is a scalpel ready for decannulation?
Yes ☐

End of procedure

Has the instrument, swab, and needle count been completed and correct?
Yes ☐

Has the EVNP assessment score been completed?
Yes ☐

Has all paperwork been completed?
Yes ☐

Has the perfusionist handed over to the implanting surgeon?
Yes ☐

Have the specimens been labelled?
Yes ☐

Were there any technical problems?
No ☐
Yes ☐ _____

Debrief – what went well, what could be improved next time?

Name of perfusionist:

Signature:

Date/time:

Figure 2: Checklist used before, during, and after EVNP in centre 1. N/A – not applicable